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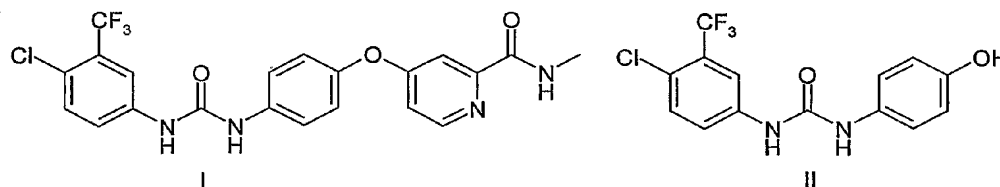
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(54) Title: NOVEL PROCESS FOR THE PREPARATION OF SORAFENIB



(57) Abstract: A novel and improved process for the preparation of sorafenib (4-(4-(3-(4-chloro-3-(trifluoromethyl)phenyl)ureido)phenoxy)-N-methylpicolinamide) of formula I involving a novel intermediate of formula II as key intermediate is disclosed. Sorafenib tosylate, available in the market as Nexavar is a multiple kinase inhibitor targeting both RAF kinase and receptor tyrosine kinase that promote angiogenesis.

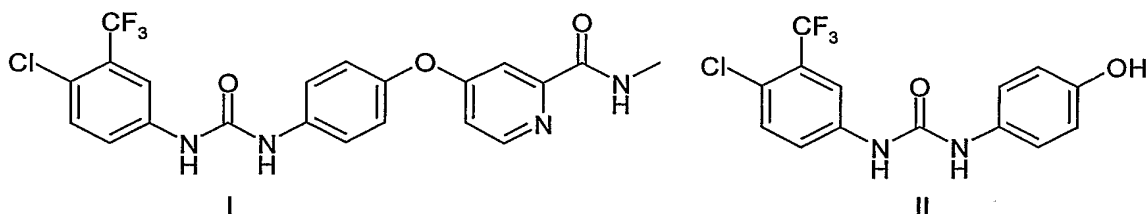


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NOVEL PROCESS FOR THE PREPARATION OF SORAFENIB

FIELD OF INVENTION

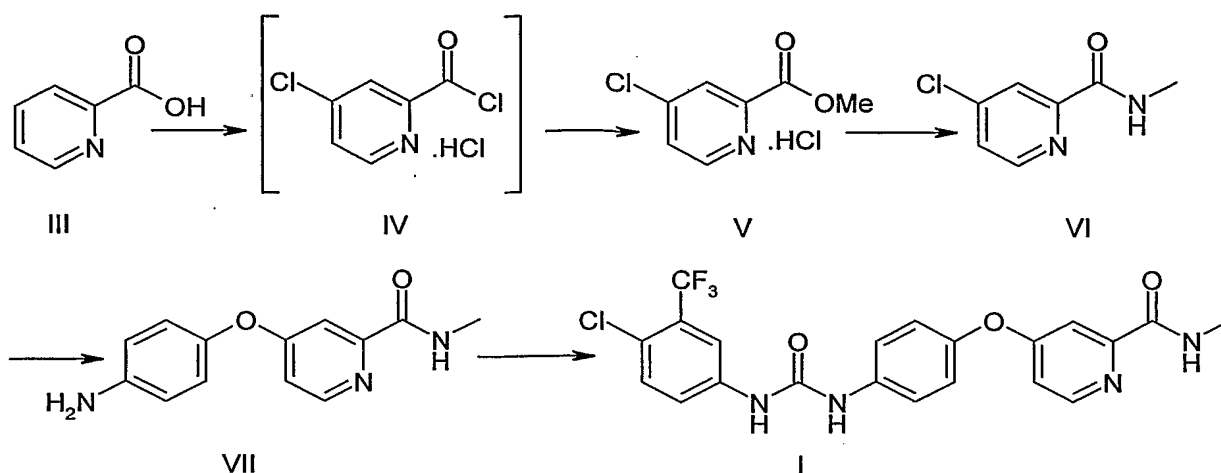
Present invention relates to a novel and improved process for the preparation of sorafenib (4-(4-(3-(4-chloro-3-(trifluoromethyl)phenyl)ureido)phenoxy)-N-methylpicolinamide) of formula I involving a novel intermediate of formula II. Compound of formula II is a key intermediate used in the synthesis of sorafenib of formula I.



Sorafenib is a multiple kinase inhibitor targeting both RAF kinase and receptor tyrosine kinase that promote angiogenesis. Clinical development of sorafenib is reviewed in Expert Opin. Pharmacother., 7, 453-461 (2006). Sorafenib is available in the market as tosylate salt under the brand name Nexavar.

BACKGROUND OF INVENTION

Sorafenib and its pharmaceutically acceptable salts and solvates are reported for the first time in WO0041698 (corresponding US 03139605) by Bayer. In the literature only one route is disclosed for the preparation of sorafenib. According to this route (Scheme-I), picolinic acid of formula III is reacted with thionyl chloride to give the 4-chloro derivative which on treatment



Scheme-I

with methanol gave the methyl ester of formula V. Compound of formula V is reacted
 5 with methylamine to get the corresponding amide of formula VI. Compound of formula
 VI is reacted with 4-aminophenol to get the ether derivative of formula VII. Compound
 of formula VII is reacted with 4-chloro-3-trifluoromethylphenylisocyanate to get sorafenib
 base of formula I. Overall yield of sorafenib in this process is 10% from commercially
 available 2-picolinic acid of formula II. Main drawback in this process is
 10 chromatographic purification of the intermediates involved in the process and low yield
 at every step.

Donald Bankston's (Org. Proc. Res. Dev., 2002, 6, 777-781) development of an
 improved synthesis of the above basic route afforded sorafenib in an overall yield of 63%
 15 without involving any chromatographic purification. Process improvements like
 reduction of time in thionyl chloride reaction; avoid the isolation of intermediates of
 formulae IV and V, reduction of base quantity in p-aminophenol reaction, etc lead to the
 simplification of process and improvement in yield of final compound of formula I.

20 Above mentioned improvements could not reduce the number of steps in making
 sorafenib of formula-I. In the first step all the raw materials are charged and heated to
 target temperature (72°C). Such a process on commercial scale will lead to sudden
 evolution of gas emissions such as sulfur dioxide and hydrogen chloride. Also, in the

aminophenol reaction two bases (potassium carbonate and potassium t-butoxide) were used in large excess to accomplish the required transformation.

5 A scalable process for the preparation of sorafenib is disclosed in WO2006034796. In this process also above mentioned chemistry is used in making sorafenib of formula I. In the first step, catalytic quantity of DMF used in the prior art process is replaced with reagents like hydrogen bromide, thionyl bromide and sodium bromide. Yield of required product remained same without any advantages from newly introduced corrosive reagents. Process improvements like change of solvents, reagents, etc were applied in
10 subsequent steps making the process scalable. Overall yield of sorafenib is increased to 74% from the prior art 63% yield. Purity of sorafenib is only 95% and was obtained as light brown colored solid.

Main drawbacks in this process are production of low quality sorafenib and requirement of corrosive and difficult to handle reagents such as thionyl bromide and hydrogen
15 bromide. Also, there is no major improvement in the yield of sorafenib.

Keeping in view of the difficulties in commercialization of the above-mentioned process for the preparation of sorafenib, we aimed to develop a simple and economical process for commercial production of sorafenib.
20

We observed that a promising approach for a process for the preparation of sorafenib would be to (a) avoid the usage of costly and difficult to handle reagents like hydrogen bromide and thionyl bromide used in the first step of the process.

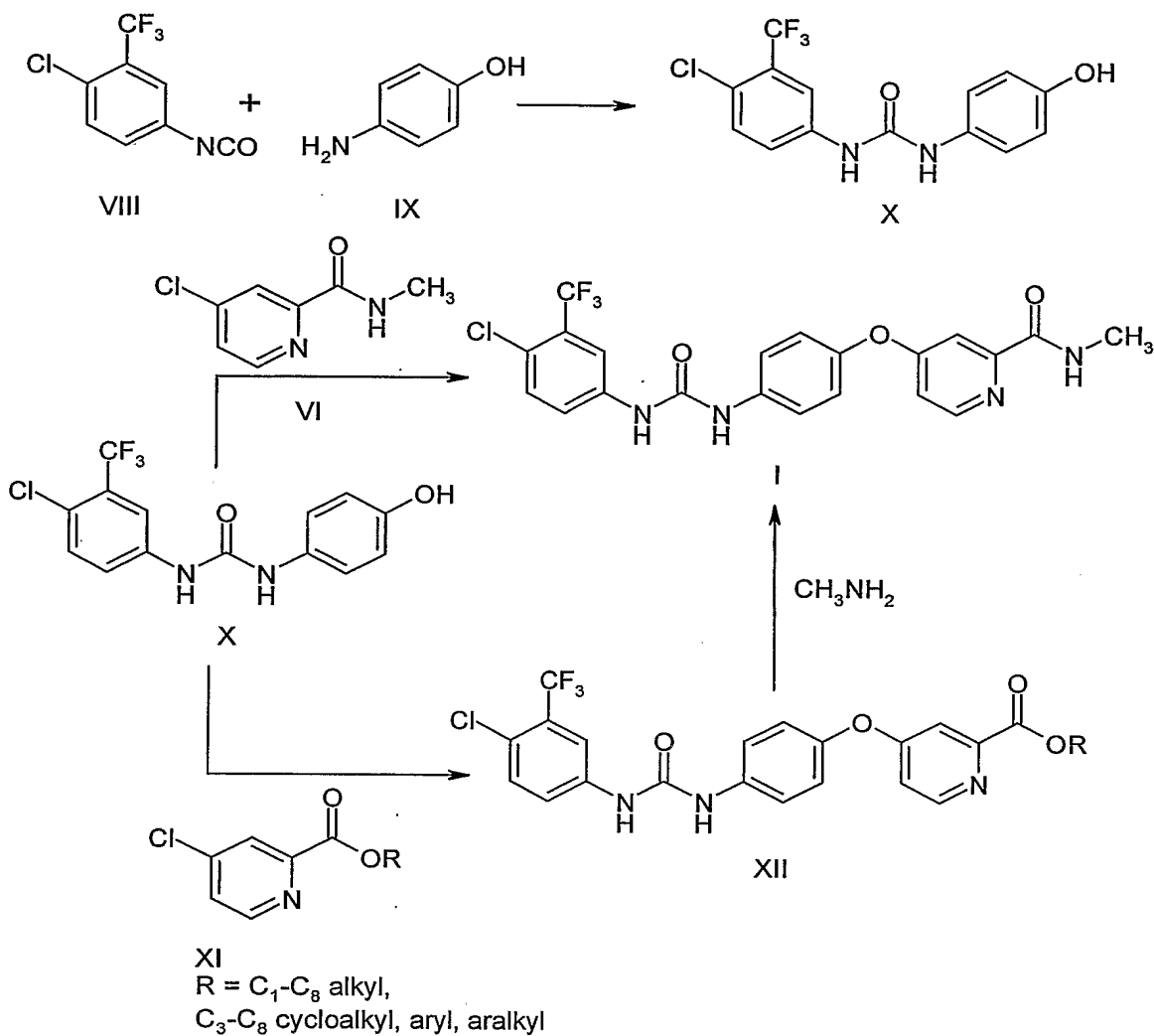
25 Accordingly, the main objective of the present invention is to provide an improved process for the preparation of sorafenib, which is commercially applicable.

Another objective of the present invention is to provide an improved process for the preparation of sorafenib avoiding the linear route with a shorter and convergent route.
30

Still another objective of the present invention is to provide an improved process for the preparation of sorafenib with >99% quality.

PROCESS OF THE PRESENT INVENTION

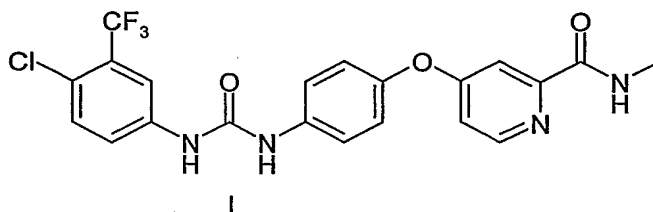
- 5 The present invention has been developed based on our finding that the reaction of 4-chloro-3-trifluoromethylphenylisocyanate of formula VIII with of 4-aminophenol of formula IX produces exclusively the novel urea derivative (N-(4-chloro-3-trifluoromethylphenyl)(4-hydroxyphenyl)-carboxamide) of formula X without the formation of any carbamate (N-(4-chloro-3-trifluoromethyl-phenyl)(4-aminophenyl)carboxamide) derivative (Scheme-II). Reaction of this novel urea derivative
10 with 4-chloro-N-methylpyridine-2-carboximide of formula VI in the presence of a base yielded the required sorafenib in high yield and purity.



Scheme-II

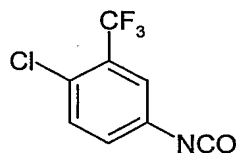
Alternatively, compound of formula X is reacted with ester derivative of formula XI in
 5 the presence of a base in a solvent medium to get novel esters of formula XII. Reaction of
 ester compound of formula XII with methylamine yielded the required sorafenib of
 formula I.

Accordingly, process of the present invention provides a novel process for the
 10 preparation of sorafenib of formula I,



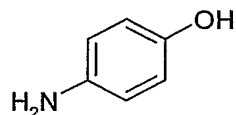
which comprises:

- (i) Reaction of the isocyanate of formula VIII,



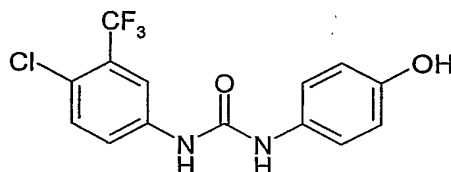
VIII

- 5 with 4-aminophenol of formula IX,



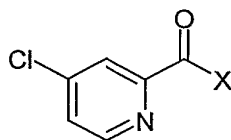
IX

or its acid addition salt in the presence of a solvent, inert towards isocyanate at a temperature above 15°C to get the compound of formula X,



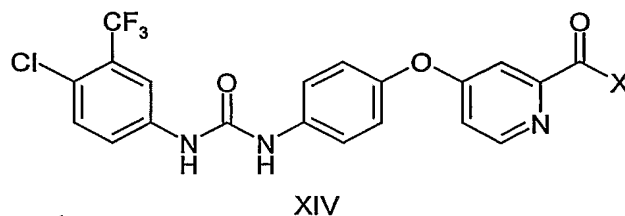
X

- 10 (ii) Reaction of compound of formula X with compound of formula XIII,



XIII

wherein X = NHCH₃, O-C₁-C₈ alkyl, O-C₃-C₈-cycloalkyl, O-aryl, O-alkylaryl or its acid addition salt in an organic solvent medium in the presence of a base at 25-120°C to get the compound of formula XIV,



wherein X = as defined above

- (iii) Reaction of compound of formula XIV (when X is not a methylamino group) with aqueous methylamine to get sorafenib of formula I

5

In a preferred embodiment of the present invention the isocyanate of formula VIII is reacted with 4-aminophenol of formula IX or its acid addition salt in the presence of a solvent, inert towards isocyanate at a temperature above 15°C. In case of acid addition salt of 4-aminophenol a neutralizing agent such as triethylamine, inert towards isocyanate is used to liberate the base.

10

In a preferred embodiment of the present invention compound of formula X is reacted with compound of formula XI in a solvent such as DMF, DMAc, DMSO, THF, dioxane, toluene, cyclohexane, acetonitrile. Base used in the reaction is selected from sodium or potassium alcoholate or sodium or potassium hydroxide, carbonate, bicarbonate, sodium hydride, etc. Temperature of the reaction is in the range of 25-120°C.

15

In a preferred embodiment of the present invention compound of formula VI is prepared from 2-picolinic acid of formula III. 2-Picolinic acid of formula III is reacted with thionyl chloride in the presence of catalytic amount of DMF and in a solvent medium at 60-80°C to get the acid chloride of formula IV. The acid chloride of formula IV thus obtained is reacted in situ with an alcohol to get the corresponding ester derivative of formula XI. The ester derivative of formula XI is reacted with methanolic methylamine to get the corresponding amide of formula VI.

25

According to the present invention sorafenib base is produced in more than 80% yield with more than 99% purity by HPLC.

Present invention provides novel compound of formula X.

The details of the invention are given in the Examples given below which are provided to illustrate the invention only and therefore should not be construed to limit the scope of the present invention.

EXAMPLES

Example 1

Preparation of 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(4-hydroxyphenyl)urea

10 Into a 250 ml, four-necked RB flask was charged 10 g of 4-aminophenol and 100 ml of toluene. A solution of 4-chloro-3-(trifluoromethyl)phenyl isocyanate (20.4 g) in toluene (50 ml) was added to the reaction mass at 25-30°C. The reaction mass was stirred at room temperature for 16 h. The reaction mass was filtered and washed the solid with 50 ml of toluene. The wet material was dried in the oven at 50-60°C to get 29.8 g of title
15 compound as white solid. M.P. is 218-222°C. IR (KBr): 3306, 1673, 1625, 1590, 1560, 1517, 1482, 1435, 1404, 1328, 1261, 1182, 1160, 1146, 1125, 1095, 1032, 884, 849, 832, 812, 766, 746, 724, 683, 539 and 434 cm⁻¹.

Example 2

Preparation of sorafenib tosylate

20 Into a 100 ml, three-necked RB flask was charged 2.0 g of 1-(4-chloro-3-(trifluoromethyl)-phenyl)-3-(4-hydroxyphenyl)urea and 10 ml of DMF. Potassium tert-butoxide (2.3 g) was added to the reaction mass and stirred for 45 min at RT. 4-Chloro-N-methylpicolinamide (1.14 g) and potassium carbonate (0.42 g) were added to the reaction
25 mass and heated to 80°C. The reaction mass was maintained at 80-85°C for 8 h and cooled to 30°C. The reaction mass was poured into water and extracted with ethyl acetate. Ethyl acetate layer was washed with water, brine and dried over sodium sulphate. Solvent was distilled of under reduced pressure.

30 The crude compound (4.7 g) was dissolved in 10 ml of IPA and added 1.9 g of p-toluenesulfonic acid. The reaction mass was stirred at RT for 15 h and filtered. The wet

solid was washed with 10 ml of IPA and dried at 50-60°C to get 3.4 g of title compound as off-white crystalline solid.

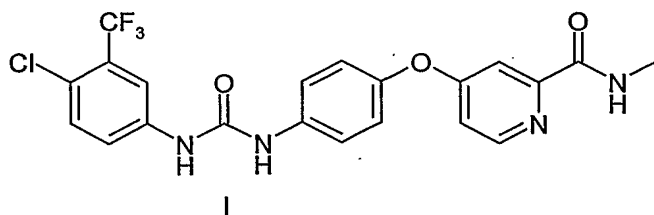
Advantages of present invention:

- 5 1. Present process is shorter and simpler.
2. Present process produces sorafenib in high yield (>80%) and high purity (>99%).
3. Present process uses a novel intermediate of formula-X.
4. Present process is economically and commercially viable.

10

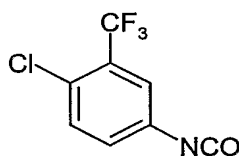
WE CLAIM:

1. A novel process for the preparation of sorafenib of formula I,



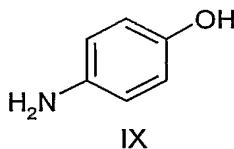
which comprises:

5 (i) Reaction of the isocyanate of formula VIII,

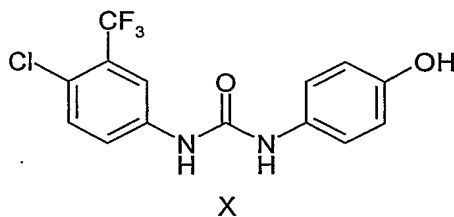


VIII

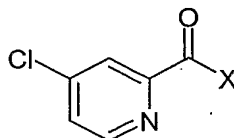
with 4-aminophenol of formula IX,



or its acid addition salt in the presence of a solvent, inert towards isocyanate at
10 a temperature above 15°C to get the compound of formula X,



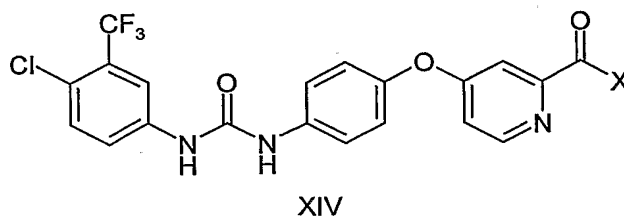
(ii) Reaction of compound of formula X with compound of formula XIII,



XIII

wherein X = NHCH₃, O-C₁-C₈ alkyl, O-C₃-C₈-cycloalkyl, O-aryl, O-alkylaryl

or its acid addition salt in an organic solvent medium in the presence of a base at 25-120°C to get the compound of formula XIV,



wherein X = as defined above

- 5 (iii) Reaction of compound of formula XIV (when X is not a methylamino group) with aqueous methylamine to get sorafenib of formula I

2. The process according to claim 1 wherein the inert solvent used in step (i) is selected from methylene chloride, chloroform, toluene, cyclohexane, heptane, acetonitrile, acetone, tetrahydrofuran, preferably methylene chloride, toluene or acetone.

10

3. The process according to claims 1 and 2 wherein the solvent used in step (ii) is selected from DMF, DMAc, DMSO, THF, dioxane, toluene, cyclohexane, acetonitrile, preferably DMF or toluene or a mixture of both.

15

4. The process according to claims 1-3 wherein the base used in step (ii) is selected from sodium or potassium alcoholate, sodium or potassium hydroxide, carbonate, bicarbonate, sodium hydride, preferably sodium or potassium alcoholate with or without sodium or potassium carbonate.

20

5. The process according to claims 1-4 wherein the preferred temperature of reaction in step (ii) is 40-80°C.

6. The process according to claims 1-5 wherein the amount of methylamine used in step (iii) is 1-6 molar equivalents, preferably 1-4 molar equivalents.

25

7. Pharmaceutical compositions comprising sorafenib prepared according to the present invention or its salts for the treatment of RAF kinase and receptor tyrosine kinase promoted angiogenesis.